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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,387	12/12/2001	Kevin P. Baker	GNE.2830P1C54	9861

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Ginger R. Dreger
Knobbe Martens Olson & Bear
Sixteenth Floor
620 Newport Center Drive
Newport Beach, CA 92660

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,387	BAKER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 28-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 28-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 28-47 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of nucleic acids which encode a protein termed Pro-1382 (SEQ ID NO: 220).

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. There are two cited utilities in the specification for this protein. The first utility is in the assay 92, paragraph 4250, in which the protein was positive in a mouse kidney mesengial cell proliferation assay. The second utility is assay 117, paragraph 4269, in which the protein was positive induction of pancreatic B-cell precursor proliferation. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 1382 antibodies. A review of the specification and of the prior art finds no well established utilities for unknown proteins whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the PRO 1382 nucleic acids which comprise SEQ ID NO: 219 and encode a protein of SEQ ID NO: 220 which are identified in either the specification or in the prior art.

Substantial utility

Here, the evidence in the specification provided is that the the PRO 1382 protein is positive in two mouse proliferation assays. No statistical data was presented to show that the proliferation was significant in any way, with no P-value or other statistical measure to demonstrate that the proliferation was a real effect and not simply produced by chance. There is no evidence that function in these assays is relevant to any real word use, such as disease therapy. Simply because the PRO-1382 protein functions to induce two different cell types does not provide the protein, much less the antibody, with any utility whatsoever.

The mere fact that a compound effects proliferation does not provide the compound with utility, since it can be, and is in the current case, entirely unclear and unpredictable how to use the compound. This is exemplified by Ambrosi et al (Biochem. Pharmacol. (2004) 67:621-630) who notes "In conclusion, from the present study we evince that the proliferative (with sera) or quiescent (without sera) cellular phase, the specific receptor repertoire (presence or absence of TrkA), pattern of nucleoside transporters (NBTI sensitive or insensitive) and degrading enzymes and, lastly, the peculiar extracellular environment are all parameters contributing to the final outcome of extracellular purines administration, in terms of either cell death, survival or differentiation. This unpredictability of effects is particularly noteworthy *in vivo*, when all

the biological parameters concerned with extracellular purines cannot be easily known or controlled (see page 629, column 1)." Thus, Ambrosi recognizes and exemplifies the fact that a simple positive result in an assay does not provide a specific and predictable in vivo use for a compound which induces proliferation.

The claimed assays are not clinically relevant since there is no evidence of record that function as a mitogen in either assay will yield a protein that will function to achieve any therapeutic function. As Ambrosi shows, even where a specific compound is shown to be active in a proliferation assay, it is entirely unpredictable whether the compound will have any in vivo function or utility whatsoever. Applicant has not demonstrated a nexus between the function of the assay and the utility of the protein. The claimed nucleic acids are even further away from utility, since there is no use for an nucleic acid which encodes a protein which lacks utility. The nucleic acids have no real world context of use.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-1382 protein, lacks any substantial utility whatsoever, and solely relies upon an positive result in the two assays. However, there is no necessary relationship between the protein and any real world use, only a "positive" result in a mitogenic assay which has no real world use. So this case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-1382. As noted in the

utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for the nucleic acids which encode the PRO-1382 protein of SEQ ID NO: 220. The nucleic acids and protein have not been associated with any disease, any condition, or any other specific feature. There is no association of the protein with cancer or with any other disease. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the positive result of the protein in the two assays gives no specific utility because there is no specific use for the protein which results from these two assays. The protein is not shown to treat any disease, to correct any condition or to provide any useful information whatsoever. Therefore, there is no specific utility for this protein and the claimed nucleic acids.

The specific utility is particularly challenging in this case, where the alignment shows that the protein appears to be similar to the Cerebellin protein precursor, which is identified in the prior art as a neuropeptide not involved whatsoever in kidney or B-cell function (see Slemmon et al (PNAS (1985) 82:7145-7148) for example, who teaches that Cerebellin is involved in neurodevelopment, not in other tissues).

In fact, Mugnaini (Synapse 2:125-128 (1988) localizes the peptide to Purkinje cells, which represents a direct teaching against the utilities cited in the specification since the protein is not normally even found or associated with either kidney or B-cells, as in the disclosed proliferation assays. This art suggests that the protein functions in an entirely different way than the two disclosed assays would suggest.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility. So the nucleic acids, whose sole utility is to encode the protein, also lack utility since the protein which they encode is lacking in utility.

Claim Rejections - 35 USC § 112 – Scope of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to an nucleic acids which encode the PRO-1382 protein. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only nucleic acids which encode the particular PRO-1382 protein but also include any any nucleic acid with at least 80% sequence identity to those SEQ ID NO: 219 or which hybridize to SEQ ID NO: 219, or which are only 10 nucleotides in length.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-1382 protein and nucleic acid, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

The mere fact that a compound effects proliferation does not provide the compound with utility, since it can be, and is in the current case, entirely unclear and unpredictable how to use the compound. This is exemplified by Ambrosi et al (Biochem. Pharmacol. (2004) 67:621-630) who notes "In conclusion, from the present study we evince that the proliferative (with sera) or quiescent (without sera) cellular phase, the specific receptor repertoire (presence or absence of TrkA), pattern of nucleoside transporters (NBTI sensitive or insensitive) and degrading enzymes and, lastly, the peculiar extracellular environment are all parameters contributing to the final outcome of extracellular purines administration, in terms of either cell death, survival or differentiation. This unpredictability of effects is particularly noteworthy *in vivo*, when all the biological parameters concerned with extracellular purines cannot be easily known or controlled (see page 629, column 1)." Thus, Ambrosi recognizes and exemplifies the fact that a simple positive result in an assay does not provide a specific and predictable in vivo use for a compound which induces proliferation.

The claimed assays are not clinically relevant since there is no evidence of record that function as a mitogen in either assay will yield a protein that will function to achieve any therapeutic function. As Ambrosi shows, even where a specific compound is shown to be active in a proliferation assay, it is entirely unpredictable whether the compound will have any in vivo function or utility whatsoever. Applicant has not demonstrated a nexus between the function of the assay and the utility of the protein. The claimed nucleic acids are even further away from utility, since there is no use for nucleic acids which encode a protein which lacks utility.

The specific utility is particularly challenging in this case, where the alignment shows that the protein appears to be similar to the Cerebellin protein precursor, which is identified in the prior art as a neuropeptide not involved whatsoever in kidney or B-cell function (see Slemmon et al (PNAS (1985) 82:7145-7148) for example, who teaches that Cerebellin is involved in neurodevelopment, not in other tissues).

In fact, Mugnaini (Synapse 2:125-128 (1988) localizes the peptide to Purkinje cells, which represents a direct teaching against the utilities cited in the specification since the protein is not normally even found or associated with either kidney or B-cells, as in the disclosed proliferation assays. This art suggests that the protein functions in an entirely different way than the two disclosed assays would suggest.

So it is entirely unpredictable how one would use this protein in any context whatsoever.

Working Examples

The specification has two working examples showing that the protein has positive results in two mitogenic tests. However, the working examples fail to show how the protein would be used, and only show that the protein can, at some level which is not disclosed by the specification, induce some level of cell proliferation. It is not clear from the specification if this activity is specific to some function of the protein or is due to some indirect effect.

Guidance in the Specification.

The specification provides no specific or substantial uses for the PRO-1382 protein. The specification does generically teach that the protein may be used in further research, such as in generation of antibodies, but provides no specific and substantial use for the protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112 – Written Description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 28-37 and 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification, since the claims are not limited to any particular SEQ ID NO, but are open to a nucleic acid that ranges from 80% to 99% identical to SEQ ID NO: 219, without any guidance on conserved portions of the protein

structure. Further, the claims encompass "hybridization" language without any correlative function as required by the utility guidelines.

Most significantly, the genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID No 219. Thus, applicant has express possession of only one particular nucleic acid sequence in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains.

There is no showing or evidence which links structural limitations or requirements to any particular functional limitations. Further, these claims encompass alternately spliced versions of the nucleic acids, allelic variants including insertions and mutations, nucleic acids which encode inactive precursor proteins which have a removable amino terminal end, and only specific nucleic and amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may

> achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the nucleic acids as having 80%-99% sequence identity to SEQ ID NO: 219 lacks any specific structure, since it lacks the correlation between structure and function that is at the heart of the caselaw and of the written description guidelines.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound without identifying the structure function relationship of the compound, so that the compound is claimed solely its nucleic acid sequence related 80%-99% to SEQ ID NO: 219 without any correlative function to delimit the structure.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention,

with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise SEQ ID NO 219. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Urade et al (Proc. Natl. Acad. Sci. (1991) 88:1069-1073).

Urade teaches an a sequence which would hybridize to SEQ ID NO: 219 and which comprises a region of more than 10 nucleotides in length that is identical to SEQ ID NO: 220 (see figure 2). This is aligned to SEQ ID NO: 219 as follows:

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Score = 91.7 bits (46), Expect = 6e-15
 Identities = 58/62 (93%)
 Strand = Plus / Plus


Query: 418 cagaacgacacggagcccatcgtgctggagggcaagtgtctggtggtgtgcgactcgaac 477
           ||||| || ||||||||||||||||||||||||||| ||||||||||||||||| |||
Sbjct: 378 cagaatgagacggagcccatcgtgctggagggcaagtgcctggtggtgtgcgactccaac 437

Query: 478 cc 479
           ||
Sbjct: 438 cc 439
```

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637